REMARKS

A. Status of the Claims

Claims 1-8 were pending in the case at the time of the Office Action, with claims 6 and 7 having been previously withdrawn from consideration. Claims 1 and 2 have been amended in, and claims 5-8 have been canceled without prejudice or disclaimer. New claims 9-10 have been added. Thus, claims 1-4, 9 and 10 are presented for reconsideration.

Claims 1-5 and 8 stand rejected anticipated by Dobie *et al.* and by Kufe *et al.* Claims 1-5 and 8 also stand rejected as obvious over Dobie *et al.* in view of Tuschl *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

B. Rejections Under 35 U.S.C. §102

1. Dobie *et al.*

Claims 1-5 and 8 stand rejected as anticipated by Dobie *et al.* Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite that the MUC-1 antagonist is an siRNA. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

2. Kufe *et al.*

Claims 1-5 and 8 stand rejected as anticipated by Kufe *et al.* Applicants traverse.

Upon evaluation of the instant application with the Kufe *et al.* application, the present applicants have determined that Steven Weitman should be named as an inventor on the instant application for at least the subject matter of the Kufe *et al.* application being cited against the present claims. Applicants are in the process of preparing the necessary documents to add Dr. Weitman as an inventor. These documents will be submitted shortly, allowing reconsideration

and withdrawal of the rejection on the grounds that Kufe *et al.* is not §102(e) prior art "by another."

C. Rejection Under 35 U.S.C. §103

Claims 1-5 and 8 stand rejected as obvious over Dobie *et al.* in view of Tuschl *et al.* According to the examiner, it would have been obvious to substitute the antisense molecule of Dobie *et al.* with the siRNA of Tuschl *et al.*, thereby arriving at the presently claimed invention Applicants traverse.

1. Lack of Motivation

Dobie focuses on antisense oligomeric compounds, particularly antisense oligonucleotides, to downregulate MUC1 expression, and use of these compounds in the treatment of diseases associated with expression of MUC1. See, *e.g.*, title, abstract, and col. 5, lines 57-61. Dobie teaches antisense as being "preferred" for its methods, and focuses almost exclusively on antisense technology. See Dobie, col. 6, lines 21-23. Dobie also teaches numerous antisense oligonucleotides that inhibit expression of the MUC1 gene. *See, e.g.*, Table 1, col. 48 – 51. It teaches that antisense provides "specificity and sensitivity" which can be "harnessed by those of skill in the art for therapeutic uses." Col. 9, lines 38-39.

While Dobie may teach an antisense oligonucleotide that hybridizes to positions 585-604 of SEQ ID NO:10, it does not provide any teaching or suggestion to apply RNA interference to downregulate MUC1, or to use of any double-stranded RNA to downregulate MUC1. The The examiner argues that Tuschl provides motivation to one of ordinary skill in the art to substitute RNA interference with the antisense technology of Dobie. Applicant disagrees.

First, thought siRNA is stated to be a powerful tool, and in the system utilized in Tuschl to work at lower levels than antisense, there is no guarantee that such will work the same way in

all systems. It is critical to note that the Tuschl data are in *D. melanogaster* – not even a mammalian system, and certainly not in human cells. Thus, the examiner's sweeping statement that Tuschl obviates the use of any siRNA for use in any mammalian system for any purpose is simply not supported.

For each of the foregoing reasons, one of ordinary skill in the art would not have been motivated to substitute the antisense compounds of Dobie with the double-stranded RNA of Tuschl. Further, even if the references were so combined, there was no likelihood that a successful inhibition or MUC-1 would have resulted, as explained further, below.

2. Lack of Likelihood of Success

Also, one of ordinary skill in the art would not assume that a successful antisense approach could be duplicated with RNA interference. Antisense technology, as disclosed by Dobie, relies on the hybridization of a nucleic acid – usually DNA and always single-stranded – to a target sequence – almost always an RNA – to inhibit translation. RNAi works in a completely different fashion – double-stranded RNA is provided to a cell that results in cleavage of target RNA.

In a declaration filed a related application (First Kufe Declaration), one of the present inventors points out differences between "interference RNA" and "antisense RNA." First Kufe Declaration, ¶13. Citing Bumcrot *et al.* (Exhibit 20 of the First Kufe Declaration), he notes that "[i]n RNAi, the target mRNA is enzymatically cleaved, leading to decreased abundance of the corresponding protein." Exhibit 20 of the First Kufe Declaration, page 711. Further, the interfering RNA is a "double-stranded RNA." See Exhibit 20 of the First Kufe Declaration, page 711, and FIG. 1. In RNA interference, long double-stranded RNA (dsRNA) is cleaved into small interfering RNA (siRNA). See Exhibit 20 of the First Kufe Declaration, page 712, and FIG. 1.

This mechanism is ***entirely distinct*** from gene inhibition using antisense RNA, where the antisense RNA is a single-stranded RNA molecule.

Thus, antisense technology works in a ***completely*** different fashion than RNAi, and thus one would not be able to conclude, without more, that success in the former would translate to success with the latter, particularly in view of the teachings of Hammond and Elbashir, which suggest that the technique that is not well-established for down-regulating gene expression.

In *Takeda Chemical v. Alphapharm*, the Federal Circuit held that in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda Chem. Indus. V. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). In the instant case, the examiner has not provided any reason that would have led a chemist to modify the antisense oligonucleotide of Dobie into a double-stranded RNA complex. Double-stranded RNA complexes are structurally distinct from the single-stranded molecules of Dobie. Further, as discussed above, antisense technology, which involves single stranded molecules, works in a completely different fashion than RNA interference, which involves double-stranded RNA. Thus, there being no motivation for a chemist to modify the compounds of Dobie into the compounds of the claimed invention, there can be no *prima facie* case of obviousness.

To further support this line of argument, applicants cite to another declaration of the inventor (Third Declaration of Dr. Kufe) from the same related case as mentioned above. Dr. Kufe cites to Miyagishi *et al.* (Antisense and Nucleic Acid Drug Development 13:1-7, 2003; Exhibit 1 of Third Declaration of Dr. Kufe). Third Declaration of Dr. Kufe, ¶¶5-6. Miyagishi *et al.* compared the effects of antisense antisense oligonucleotides and siRNAs directed against the same targets in mammalian cells. The targets were six sites in the firefly gene for luciferase.

Results showed that there were significant differences in the suppressive effects at each of the target sites. See Miyagishi *et al.*, page 5, left column, and FIG. 2A and FIG. 3. As can be seen from FIG. 2A and FIG. 3, the correlation coefficient between the results for antisense ODN's and siRNA was low (0.42). In view of this evidence, a person of ordinary skill in the field, who would have been familiar with Miyagishi *et al.*, would have understood that the effects of antisense technology are not necessarily the same as the effects with RNA interference.

Therefore, one of ordinary skill in the art would not have any reasonable expectation of success that RNA interference could be successfully applied in down-regulating MUC1. In view of the foregoing, it is respectfully submitted that the claims are not obvious as argued by the examiner. Reconsideration and withdrawal of the rejection are respectfully requested.

D. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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